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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,396	07/10/2001	Keith D. Allen	R-359	9463

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EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 11/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,396	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,13-16,30-32 and 34-48* is/are pending in the application.

4a) Of the above claim(s) *1-4,13-16,30-32,and 34-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *15 August 2003* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment filed on 08/15/2003 has been entered. Claims 5-12,17-19 and 33 have been canceled. Claims 36-48 have been added. Claims 1-4,13-16,30-32,34-35 and 36-48 are pending and claims 36-48 are under consideration in the instant action.

Election/Restrictions

Claims 1-4,13-16,30-32 and 34-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Drawings

The drawings were received on 08/15/2003. These drawings are acceptable.

Sequence Compliance

The instant application is now sequence compliant.

Claim Rejections - 35 USC § 101/112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Newly added claims 36-48 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

The claims are directed to a transgenic mouse whose genome comprises a homozygous disruption in glucocorticoid-induced receptor gene, wherein the mouse exhibits hyperactivity, reduced anxiety, decreased propensity toward behavioral despair or decreased propensity toward depression (claims 36-40 and 48) and methods of making said mouse (claim 47). Claims are further directed to cells or tissues isolated from the same mouse (claim 41). Claims are also directed a mouse comprising a heterozygous disruption in glucocorticoid-induced receptor gene (claims 42-46).

The instant specification has contemplated that the nucleotide sequence set forth in SEQ ID NO: 1 encodes a glucocorticoid-induced receptor. The instant specification has further contemplated that disruption of the nucleotide sequence set forth in SEQ ID NO: 1 in a mouse will produce a phenotype associated with a disruption of a glucocorticoid-induced receptor. The instant specification has purported that such mice may be used to identify agents that modulate or ameliorate a phenotype associated with a disruption in SEQ ID NO: 1. See page 19, line 24-page 20, line 2.

The specification has provided general assertions that the claimed transgenic mice may be used to identify agents that affect a phenotype related to the mice. As such, the asserted utility, for the transgenic mouse encompassed by the claims, of screening agents that may affect

a phenotype of said mouse as provided by the instant specification and encompassed by the claims, does not appear to be specific and substantial. The asserted utility does not appear specific and substantial to the skilled artisan since the evidence of record has not provided any suggestion of a correlation between a homozygous disruption of a glucocorticoid-induced receptor gene, reduced anxiety, decreased propensity toward behavioral despair or decreased propensity toward depression, and any disease or disorder. Since the evidence of record has not provided a correlation between reduced anxiety, decreased propensity toward behavioral despair or decreased propensity toward depression and any disease or disorder, the utility of identifying agents that affect reduced anxiety, decreased propensity, toward behavioral despair or decreased propensity toward depression is not apparent. The evidence of record has not provided any other utilities for the transgenic mouse encompassed by the claims that are specific and substantial.

The instant specification has disclosed a transgenic mouse whose genome comprises a disruption in SEQ ID NO: 1, wherein the mouse exhibits hyperactivity, reduced anxiety, decreased propensity, toward behavioral despair or decreased propensity toward depression. See pages 53-54. The instant specification has discussed that the animals and cells of the instant invention can be used as models of disease (refer to pages 18-19). Specifically, the specification states that agents can be identified on the basis of their ability to affect at least one phenotype associated with a disruption in a glucocorticoid-induced receptor gene (page 19, lines 24-26). However, the evidence of record, while contemplating that the phenotypes inhibited by the claimed transgenic mice are associated with a disease, does not provide a correlation between the phenotypes of the claimed mouse and any disease or disorder, leaving the skilled artisan to speculate and investigate the uses of the transgenic mouse encompassed by the claims. While

the art at the time of filing taught using mice displaying phenotypes of increased anxiety or depression for screening agents for therapeutic activity (Gass, 2001, Physiology and Behavior, Vol. 73, pp. 8111-825, specifically, page 815-816, section 5 and page 820-821m section 8). The utility of these mice, however, does not reflect a use for the claimed mice displaying an opposite phenotype indicating decreased propensity toward depression, decreased propensity for behavioral despair or reduced anxiety. Mice with decreased propensity for anxiety or depression would not offer the same utility in screening for therapeutic agents to treat diseases such as anxiety or depression and the specification fails to correlate decreased propensity for anxiety or depression with any other disease. Furthermore, as taught by Gass et al., the usefulness of mutant mice as models of depression is not even clear without assessing that they specifically reflect human depression. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the transgenic mouse encompassed by the claims. In light of the above, the skilled artisan would not find the asserted utility of the transgenic mouse encompassed by the claims to be specific and substantial.

Claims 6,8-10,23, 29-32 and 35-39 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Upon overcoming the utility and enablement rejections set forth above, the following issues of enablement under 35 USC 112-1st paragraph must also be addressed.

1) The specification fails to enable disrupting any glucocorticoid-induced receptor gene in a mouse or any other species or a cell other than a mouse cell. The claims lack a modifier before the phrase "endogenous mouse glucocorticoid-induced receptor gene" and therefore the breadth of the claims includes mouse glucocorticoid-induced receptor genes other than that set forth by SEQ ID NO:1. The evidence of record teaches only one glucocorticoid-induced receptor gene (Harrigan, 1991, Molecular Endocrinology, Vol. 5, pages 1331-1338; and the instant specification, SEQ ID NO:1). The specification does not provide adequate guidance for determining any other glucocorticoid-induced receptor gene or that other glucocorticoid-induced receptor genes have the same function as the glucocorticoid-induced receptor gene disclosed. Inserting the word "the" prior to the phrase "endogenous mouse glucocorticoid-induced receptor gene", would overcome this rejection.

2) The rejection based on the specification failing to enable making or using any transgenic mouse comprising a disruption in the glucocorticoid-induced receptor gene wherein the mouse is of any genetic background and wherein the mice exhibit hyperactivity, reduced anxiety, decreased propensity towards behavioral despair, or decreased propensity toward depression is maintained for reasons of record set forth on pages 12-14 of the previous office action.

Applicant's arguments with respect to this aspect of the rejection have been fully considered and are not considered persuasive. Applicant argues that one of skill in the art would be able to easily determine the phenotype of the claimed mice regardless of genetic background. However, the claims encompass generating the claimed mice with specific behavioral phenotypes using mice of any genetic background. As discussed in the previous office action

(refer to paragraph bridging pages 12-13), the state of the art was that genetic background has a significant effect on the development of the claimed phenotypes in knockout mice (refer to Crabbe and Yoshikawa). Furthermore, Liu taught that the response on the tail suspension test varies among different strains of mice (2001, Biological Psychiatry, Vol. 49, pages 575-581, specifically, page 576, column 1, lines 17-19; page 577, column 2, Results paragraph 1). More specifically, Mayorga taught that the occurrence of tail climbing in C57BL/6 mice in response to the tail suspension test, which is not observed in other strains, is an important consideration and limitation when using this strain in the tail suspension test (2001, Psychopharmacology, Vol. 155, pages 110-112, specifically page 110, paragraph bridging columns 1 and 2; page 111, column 2, paragraph 2). Mayorga also teaches that this phenomenon should be considered when planning experiments to characterize potential antidepressants in mice using the tail suspension test and in the choice of mouse strain for the generation and testing of knockout mice (page 111, column 2, last 5 lines). The reports of Crabbe, Yoshikawa, Liu and Mayorga are each evidenced in the specification as N0 generation animals did not display results in the open field test or the tail suspension test indicating they may be more hyperactive and less anxious or that they may have less of a propensity towards behavioral despair or depression than their wild-type littermates; however, N1 generation mice did display such results (page 53, last paragraph; Table 1; page 54, lines 4-9). The difference in the N0 and N1 generation animals is only the genetic background; N1 mice were backcrossed to the C57BL/6 strain whereas the N0 mice were not (page 53, lines 16-21). Furthermore, the specification states that "The discrepancy in the results observed in the Open Field and Tail Suspension Tests between generations may reflect differences in the background strains used to generate the mice" (page 54, lines 13-15). Thus, the

specification teaches that genetic background alters the phenotype of mice comprising a disruption in the glucocorticoid-induced receptor gene and fails to teach how to generate the claimed phenotypes in the mice of any genetic background as broadly encompassed by the claims.

3) The specification fails to enable the method of claim 47. The term "murine" in steps (a) and (b) encompass both mouse and rat species. The method is drawn to generating a mouse. The specification does not teach generating a mouse using an ES cell derived from any species other than mouse. Furthermore, as stated in the previous office action, the art at the time of filing was that totipotent ES cells that contribute to the germline had not been identified for any species other than mouse (refer to Mullins; Campbell and Wilmut). Therefore, ES cells derived from non-mouse species cannot be used to generate a transgenic animal. Claim 47 should be limited to producing a transgenic mouse using mouse embryonic stem cells.

4) The breadth of claims 42-48 is such that they encompass chimeric animals (genetic mosaics) wherein only a portion of the cells of the animal comprises the claimed genetic disruption. The specification teaches making transgenic animals whose genome comprises a homozygous disruption in the glucocorticoid-induced receptor gene in all somatic and germ cells wherein the mice display hyperactivity, reduced anxiety, decreased propensity towards behavioral despair, or decreased propensity toward depression. The specification does not teach a chimeric animal with these phenotypes. The method of making genetic mosaic animals is such that each resulting chimera is comprised of a different, unpredictable ratio of cells of various genotypes. This ratio cannot be predetermined. Furthermore, the spatial distribution of cells of each genotype cannot be predetermined. Therefore, the phenotype of chimeric animals is not

only dependent upon the genotype of the cells (which is unpredictable as set forth by the state of the art outlined on pages 8-10 of the previous office action; for example see Leonard; Moens;Griffiths, Mullins 1989,1990; Taurog) but is also dependent upon the spatial distribution of the cells and their relative population size. Thus, the phenotype of the chimeric animals encompassed by the claims is highly unpredictable. It would require undue experimentation for one of skill in the art to determine how to overcome the unpredictability associated with making chimeric animals such that the proportion and population of cells harboring a genetic alteration could be controlled in such a way as to increase the predictability of the phenotype of the resulting chimeric animal. Replacing the term "comprising" in line 1 of claims 42 and 47 with the phrase "whose genome comprises" is suggested.

5) Claims 42-48 encompass transgenic mice comprising a heterozygous disruption in the endogenous mouse glucocorticoid-induced receptor gene. As set forth in the previous office action (refer to Leonard and Griffiths), the phenotype of knockout mice is unpredictable. The specification disclosed phenotypes exhibited by some knockout mice that comprise a homozygous disruption in the glucocorticoid-induced receptor gene (pages 53-54); however, the specification does not teach a phenotype for mice comprising a heterozygous disruption in the glucocorticoid-induced receptor gene that differs from a wild-type mouse. The specification asserts that the claimed mice can be used for drug testing (pages 3-4 and 19-20), however, the specification fails to describe any phenotype for the mouse that correlates with a disease. The skilled artisan would not know how to use a transgenic knockout mouse that lacks a phenotype, particularly because the instant specification has not provided uses for such. Given the unpredictable nature if a phenotype that results from disruption of a nucleotide sequence, it

would have required undue experimentation for the skilled artisan to use the claimed heterozygous knockout mouse that lacks a phenotype.

Newly added claims 36-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as applied to cancelled claims 5-12,17-29 and 33 for reasons of record as set forth on pages 5-6 of the previous office action mailed 03/12/2003.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The basis of the rejection that the specification fails to describe the broad genera of genes encompassed by the claims applies to the newly added claims 36-48. Applicant's arguments have been fully considered and are not found persuasive. Applicant argues that the newly added claims recite "the endogenous mouse glucocorticoid-induced receptor" (page 6, line 20), however claims 36, 42 and 47 recite "...disruption in endogenous mouse glucocorticoid-induced receptor gene" and are therefore not limiting to the mouse glucocorticoid-induced receptor described in the specification. Therefore, as stated on page 6 lines 9-15 of the previous office action, the claims can be read as being drawn to more than one mouse glucocorticoid-induced receptor gene and the specification only describes one mouse glucocorticoid-induced receptor gene.

In the instant case the mouse glucocorticoid-induced receptor genes encompassed by the claims lack a written description. The specification fails to describe what DNA molecules fall into this genus and it was unknown as of Applicants' effective filing date that any of these DNA molecules would have the property of encoding a glucocorticoid-induced receptor polypeptide having the same structural and functional properties as that encoded by SEQ ID NO:1. The claimed embodiments of glucocorticoid-induced receptor genes encompassed within the genus lack a written description. There is no evidence on the record of a relationship between the structures of the nucleotide sequences coding for a mouse glucocorticoid-induced receptor and the nucleotide sequence set forth by SEQ ID NO:1 that would provide any reliable information about the structure of DNA molecules within the genus. The claimed invention as a whole is not adequately described if the claims require essential or critical elements that are not adequately described in the specification and that is not conventional in the art as of applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641,1646 (1998).

With the exception of the sequence referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred regardless of the complexity or simplicity of the method of isolation. The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acid molecules and therefore conception is not achieved until reduction

to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by any member of the genus of genes encoding glucocorticoid-induced receptor. Therefore, only the glucocorticoid-induced receptor gene encompassed by **SEQ ID NO:1**, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that "to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention".

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The previous rejection of claims 5-10 under 35 USC 103 is withdrawn.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on Mon-Weds 6:00-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

PETER PARAS
PATENT EXAMINER

Valarie Bertoglio
Examiner
Art Unit 1632